DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
2098 Gaither Road
Rockville, MD 20850

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VIA FEDERAL EXPRESS

WARNING LETTER

Mr. Kjell Wallin
Site Manager
Perstorp Specialty
Chemicals AB
Perstorp Pharma
S-284 80 Perstorp
Sweden

Dear Mr. Wallin:

During an inspection of Perstorp Pharma, Buildings 832, 836 and 837, Perstorp, Sweden, on August 21 through 24, 2000, our investigator determined that your firm manufactures sterile wound cleaning gels and pads and powders with iodine. These are devices as defined by section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act).

The above-stated inspection revealed that these devices are adulterated within the meaning of section 501(h) of the Act, in that the methods used in, or the facilities or controls used for manufacturing, packing, storage, or installation are not in conformance with the Good Manufacturing Practice (GMP) for Medical Devices Regulation, as specified in Title 21, Code of Federal Regulations (CFR), Part 820, as listed below. Your responses, dated September 5, 2000, September 14, 2000, January 12, 2001, and January 24, 2001 to the investigator's findings were also reviewed. Comments on your response follow each observation.

1. Failure to validate with a high degree of assurance where a process cannot be fully verified, as required by 21 CFR 820.75(a). For example:

   a. Initial performance qualifications and re-evaluations using media fills have not included all worst case conditions, including duration and size of run and line stoppages for repairs or other reasons except for change over container sizes.

   b. There is no data showing the cleaning procedure is capable of removing cleaning agent residuals to the specified level of [ ] for the entire Iodosorb gel manufacturing circuit.

Your response is not adequate. For 1(a), your response omits critical information, such as: routine production of Iodosorb gel consists of [ ] of bulk that is packaged into either [ ] or [ ] Media fill batch sizes have ranged in size from [ ] The media fills do not include stoppages that simulate equipment repairs or building shutdowns. There were several instances when the air handling system had shut down or fell outside operating specifications during production. When this occurs, the procedure is to halt production and cover in-process product with plastic. None of these actions were included or simulated as part of the media fills. For 1(b), your response indicates that the cleaning validation report concluded that the cleaning procedure is capable of removing the cleaning agent, [ ] to a level less than [ ] for the entire circuit. No cleaning agent was detected in any of the samples. You admitted to errors in the values of cleaning agent remaining on samples taken during investigation but stated that the amount of cleaning agent remaining on the entire circuit is well within the specified level of less than [ ]. You stated that the cleaning procedure will be revalidated and a new report issued. The new procedures need to be submitted to us for review.

2. Failure to establish and maintain process control procedures that describe any process controls necessary to ensure conformance to specifications, as required by 21 CFR 820.70(a). For example:

   a. Alert and action levels for tube filling settling plates have not been established.

   b. Alert levels and associated actions have not been established for particulate and microbial monitoring.

Your response is not adequate. For 2(a), your response indicates that an appropriate alert limit will be applied to the settling plate results based upon a calculated average microbial contamination level with respect to the total exposure time of a sequence of settling plates used during production run. [ ] For 2(b), your response indicates that the environmental control procedures will be revised to include alert levels and instructions how to act when these levels have been exceeded. You stated that the revised procedures for 2(a) and 2(b) should have been in place by September 30, 2000. The new procedures need to be submitted to us for review.

3. Failure to establish and maintain procedures to adequately control environmental conditions, as required by 21 CFR 820.70(c). For example:

a) While environmental monitoring data are analyzed, procedures for analyzing such data to identify existing and potential causes of quality problems have not been established.

b) The class A aseptic filling area for Iodosorb gel is not monitored for non-viable particles.

c) Quantitative laminar airflow velocities are monitored for the HEPA filters in the Class A aseptic filling area only two times per year.

d) Periodic identification of recovered microorganism is not performed.

e) Periodic selective testing for mold and yeast is not performed.

Your response is not adequate. For 3(a), you acknowledged the need for additional instructions describing the analysis of data to identify existing and potential causes of problems. You stated that procedures would be revised by September 30, 2000. For 3(b), you acknowledged that particulate monitoring should be carried out wherever possible and the process documentation will be amended to carry out particulate monitoring in the Vertical Laminar Airflow (VLAF) at the start and end of each filling operation. You stated that the procedure describing the particulate measuring to be carried out should have been completed by September 30, 2000.

For 3(c), you stated that the incorporation of the Grade A VLAF's into the computerized monitoring system would be in place by December 31, 2000. For 3(d), you stated that you would amend your environmental monitoring procedures to include the periodic identification of recovered microorganisms. The procedure should have been in place by September 30, 2000 with results from baseline testing available by December 31, 2000.

For 3(e), you stated that you would amend your environmental monitoring procedures to include periodic selective testing for molds and yeast. The procedure should have been in place by September 30, 2000 with results from baseline testing available by December 31, 2000. The new procedures need to be submitted to us for review.

4. Failure to retain records for a period of time equivalent to the design and expected life of the device, as required by 21 CFR 820.180(b). For example, printouts of filter integrity test failures attributed to poor connections with the analyzer, [ ] are discarded and not retained as part of the batch record. Only the subsequent acceptable test printouts are retained.

Your response is not adequate. You agreed with this observation. The operators were informed immediately that printouts of filter integrity test failures shall be retained in the batch record. You stated that the procedure was amended and should have been in place by September 30, 2000. The new procedure needs to be submitted to us for review.

5. Failure to ensure that the Device Master Record (DMR) includes the appropriate production procedures, including production environment specification, as required by 21 CFR 820.181(b). For example, air handling system alarms require deviation reports for "major" reasons and only supervisor signature with no management or QA review for "minor" reasons. "Major" and "minor" have not been defined in established procedures.

Your response is not adequate. You acknowledged that there is no general management review of events and alarms relating to the air handling system. You stated that the procedures relating to the control of the air handling system will be amended to include a review by QA and management. You stated that the revised procedure should have been in place by September 30, 2000. The new procedure needs to be submitted to us for review.

6. Failure to establish and maintain procedures for investigating the cause of nonconformities relating to product, processes, and the quality system, as required by 21 CFR 820.100(a)(2). For example, procedures describing requirements for investigations to be conducted when action levels are exceeded have not been established.

No investigations that included identification of causes were conducted regarding the following instances where action levels were exceeded:

a. The airsampling and 5 finger microbial levels found during the processing of Lot BCA 18.
b. The settling plate microbial levels found during the processing of Lot BDD 12.

c. The 5 finger microbial levels found during the processing of Lots BDD 042, BDC 291, BDC 011, and BDA 194.

Your response is not adequate. You stated that the revised procedure should have been in place by September 30, 2000. The new procedure needs to be submitted to us for review.

7. Failure to establish and maintain procedures to identify the action(s) needed to correct and prevent recurrence of nonconforming product and other quality problems, as required by 21 CFR 820.100(a)(3). For example:

a. Procedures for corrective and preventive actions do not ensure the cause of quality problems and the actions needed to correct and prevent recurrence of such quality problems identified. For example, the cause of the failures resulting in the following complaints and deviations reports were not identified:

- Complaint 1999/05/M/26
- Deviation report for category 5 lot CDA 273
- Deviation category 6 lot ADE 251

b. Defined actions taken in response to air handling system failures and shutdowns do not identify when and what environmental monitoring is required prior to production start up.

Your response is not adequate. For 7(a), Complaint 1999/05/M/26 was regarding an empty sachet of lodoflex powder. The root cause of the complaint was not identified and the rationale for the lack of an investigation was not documented. Deviation report for category 5 lot CDA 273 was initiated because a lodosorb pad was sealed in the incorrect position. The lot was sorted and any additional units with this defect were rejected. The numbers were not documented. The root cause was not identified and the rationale for the lack of an investigation was not documented.

Deviation report for category 6 lot ADE 251 was initiated because the total recovered iodine was [ ] when the specification is [ ] The lot was rejected.

The root cause was not identified and the rationale for the lack of an investigation was not documented. You acknowledged that the deviation and complaint procedures could be clarified and will be amended to state the cause of quality problems and actions needed to correct and prevent recurrence of such quality problems. For 7(b), you stated

that the procedure would be revised to include detailed instructions of the procedures to be followed by QA, with respect to the environmental controls to be implemented prior to start up of production. You stated that both procedures should have been in place by September 30, 2000. The new procedures need to be submitted to us for review.

8. Failure to establish and maintain procedures for verifying or validating the corrective and preventive action to ensure that such action is effective and does not adversely affect the finished device, as required by 21 CFR 820.100(a)(4). For example, procedures requiring the verification or validation of the adequacy of corrective and preventive actions have not been established.

Your response is not adequate. You agreed with this observation and stated that you would update your corrective and preventive action procedures. You stated that the procedures should have been in place by September 30, 2000. The new procedures need to be submitted to us for review.

9. Failure to document corrective and preventive actions, as required by 21 CFR 820.100(b). For example:

a. There is no documentation that shows the corrective and preventive action taken in response to the in-process leak test failure of 1 unit of 5 units tested during the second ½ hour of production for lot BDC 011 extended to an evaluation of product produced at that time. An equipment adjustment was the only documented corrective action.

b. While reportedly implemented, the corrective action identified in response to the failure resulting in complaint 2000/03/M/028, (addition of weight check for Iodoflex dressing in response to missing packet in a carton) was not translated to production specifications and is not documented in any batch record.

c. All corrective and preventive actions taken in follow-up to complaint 1999/04/M/030 (open seal) were not documented. Reportedly, the foil pouches in stock were destroyed as a corrective action.

Your response is not adequate. For 9(a), with respect to the leak test failure, reportedly all tube batches produced from the beginning of 1999 to present, batch BDC011 was the only material to be identified as leaking during the in-process control. Reportedly no complaints have been received with respect to leaking tubes since production started in 1994. For 9(b), you agreed with this observation

and explained that weight check should have been introduced into the work instructions/batch record by September 30, 2000.

Also, revision of all procedures relating to the change in the corrective and preventive action system should have been in place by September 30, 2000. For 9(c), you agreed with this observation and explained that revision of all procedures relating to the change in the corrective and preventive action system should have been in place by September 30, 2000. The new procedures need to be submitted to us for review.

10. Failure to establish and maintain data that clearly describe or reference the specified requirements, including quality requirements, for purchased or otherwise received product, as required by 21 CFR 820.50(b). For example, the supplier was not informed of the category 5, lot CDE 092 deviation regarding uneven printing on the foil pouch.

Your response is adequate. You provided information to us showing that the supplier had been informed of the deviation.

This letter is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence to each requirement of the Act and regulations. The specific violations noted in this letter and in the form FDA 483 issued at the closeout of the inspection may be symptomatic of serious underlying problems in your firm's manufacturing and quality assurance systems. You are responsible for investigating and determining the causes of the violations identified by the Food and Drug Administration. If the causes are determined to be systems problems, you must promptly initiate permanent corrective actions.

Federal agencies are advised of the issuance of all Warning Letters about devices so that they may take this information into account when considering the award of contracts.

Please notify this office, in writing, within 30 working days of receipt of this letter, of the specific steps you have taken to correct the noted violations, including an explanation of each step being taken to identify and make corrections to any underlying systems problems necessary to assure that similar violations will not recur.

Please include any and all documentation to show that adequate correction has been achieved. In the case of future corrections, an estimated date of completion, and documentation showing plans

for correction, should be included with your response to this letter.

If documentation is not in English, please provide an English translation to facilitate our review.

Your response should be sent to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Enforcement I, General Surgery Devices Branch, 2098 Gaither Road, Rockville, Maryland 20850, to the attention of Wayne Q. Miller.

Sincerely yours,

Larry D. Spears
Acting Director
Office of Compliance
Center for Devices and
Radiological Health

Cc:
Mr. Jenke Hartwall
Perstorp Specialty
Chemicals AB
Perstorp Pharma
S-284 80 Perstorp
Sweden